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Sexual functioning mirrors overall men's health status, even irrespective of cardiovascular risk factors

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SUMMARY

Erectile dysfunction has been described as a sentinel marker of co-existing and undetected cardiovascular disease. Beside cardiovascular diseases, a correlation between erectile dysfunction and other major comorbidities has been also reported. The study was aimed to analyze the association between sexual functioning and overall men's health in sexually active, Caucasian-European men with new-onset sexual dysfunction. Data from the last 881 consecutive patients seeking first medical help for sexual dysfunction were cross-sectionally analyzed. The *International Classification of Diseases*, 9th revision, Clinical Modification was used to classify health-significant comorbidities, which were scored with the Charlson Comorbidity Index (CCI). A modified CCI score from which all potential cardiovascular risk factors (CCI-CV) were subtracted was then calculated for every patient. Patients were requested to complete the International Index of Erectile Function (IIEF). The main outcome of the study was the association between the IIEF domain scores and CCI, which scored health-significant comorbidities even irrespective of cardiovascular risk factors (CCI-CV). The final sample included 757 patients (85.9%) (Median age: 48 years; IQ range: 37–59). Overall, erectile dysfunction was found in 540 (71.4%) patients. Of these, 164 (21.6%) had a CCI ≥ 1 and 138 (18.2%) had a CCI-CV ≥ 1, respectively. At the analysis of variance, IIEF-Erectile Function (EF) scores significantly decreased as a function of incremental CCI and CCI-CV scores (all $p < 0.01$). At multivariable logistic regression analysis, both IIEF-EF and IIEF-total score achieved independent predictor status for either CCI ≥ 1 or CCI-CV ≥ 1, after accounting for potential confounders ($p < 0.01$). We report novel findings of a significant association between erectile dysfunction severity and overall men's health, even irrespective of cardiovascular risk factors. Thereof, erectile dysfunction severity could serve as a proxy for general men's health, thus encouraging physicians to comprehensively assess patients complaining of sexual dysfunction in the real-life everyday clinical practice.

INTRODUCTION

There is a close correlation between overall health and sex, and there exist a few clear demonstrations of how sexual activity may negatively impact the health of every individual (Dahabreh & Paulus, 2011). Conversely, a large number of studies highlighted how sexual health is linked with better overall health of an individual (Basson *et al.*, 2010; Montorsi *et al.*, 2010). More specifically, an increasing number of observations highlighted this correlation for men; indeed, erectile dysfunction (ED) has progressively emerged as a sentinel marker of overall men's health, gaining major relevance in the cardiovascular (CV) field (Gandaglia *et al.*, 2014). In this context, ED and cardiovascular diseases (CVDs) are known to share several aspects of their etiology and pathophysiology; likewise, numerous studies have clearly ascertained ED as an independent risk marker for CVDs (Montorsi *et al.*, 2003; Thompson *et al.*, 2005; Vlachopoulos *et al.*, 2007, 2013; Araujo *et al.*, 2010; Guo *et al.*, 2010; Dong *et al.*, 2011). Overall, incident ED may significantly increase the risk of CVDs, coronary heart disease (CAD), stroke, and overall atherosclerotic CV events (Vlachopoulos *et al.*, 2013). Of clinical importance, the link between ED and man's health status goes even further than the CV field, with previous studies

demonstrating a significant correlation between ED and comorbidities other than CVDs and even with all-cause mortality (Chung *et al.*, 2011; Salonia *et al.*, 2012; Banks *et al.*, 2013; Skeldon *et al.*, 2015).

In this context, preliminary data would suggest that the severity of ED may account for a lower male general health status, regardless of its etiology, configuring ED per se as a primary manifestation of an underlying disorder, thus potentially assuming the role of a sentinel marker of overall men's health also and especially in daily clinical practice (Salonia *et al.*, 2012).

To examine this hypothesis, we sought to determine whether impaired sexual functioning per se may be considered a reliable proxy of lower general health status in men irrespective of established CVDs, in a cohort of sexually active, Caucasian-European men seeking first medical help for new-onset sexual dysfunction at a single outpatient clinic.

MATERIALS AND METHODS

Patients

The analyses were based on a series of data prospectively collected from 881 consecutive sexually active, Caucasian-European patients seeking first medical help for new-onset sexual dysfunction at a single academic tertiary-referral outpatient clinic for sexual medicine from January 2000 to December 2015.

Patients were assessed with a thorough medical history, including data on health-significant comorbidities as scored with the Charlson Comorbidity Index (CCI; Charlson *et al.*, 1987), which in its original version contains 17 different disease comorbidity categories; each is allocated a weight of 1–6 based on the adjusted relative risk of 1-year mortality and summed to provide a total score. The higher the score, the more severe the burden of comorbidity. As a consequence, CCI sum is an indicator of disease burden and a strong estimator of mortality (Charlson *et al.*, 1987). We used the *International Classification of Diseases*, 9th revision, Clinical Modification (ICD-9-CM) because its coding algorithms were used to define the 17 comorbidities that constitute the most widely used CCI. A modified CCI score (defined, CCI-CV), from which all potential CV risk factors were subtracted was then calculated for all patients. Similarly, medications were recorded for each patient. Measured body mass index (BMI), defined as weight in kilograms by height in square meters, was also considered in all cases (National Institutes of Health, 1998). Hypertension, which is not taken into account by the CCI, was recorded and defined when antihypertensive medication was taken and/or for high blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic). Moreover, recreational habits, thus including smoking history, and patient's physical activity were also recorded.

Likewise, patients were assessed with a detailed sexual history. For the purpose of this study, ED was defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance (NIH Consensus Conference, 1993). According to the definition of the International Society of Sexual Medicine (ISSM; McMahon *et al.*, 2008), premature ejaculation (PE) was defined as ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 min or less (acquired PE), the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or avoidance of sexual intimacy. Low sexual desire/interest (LSD/I) was defined as an umbrella term for disorders of reduced male sexual desire, for which hypoactive sexual desire disorder (HSDD) would represent only a subtype (Rubio-Aurioles & Bivalacqua, 2013). Lastly, Peyronie's disease was defined according to the European Association of Urology guidelines for penile curvature (Hatzimouratidis *et al.*, 2012).

Moreover, to provide a frame of reference for objectively interpreting sexual functioning, patients were requested to complete the International Index of Erectile Function (IIEF; Rosen *et al.*, 1997). To interpret ED severity, we used the IIEF-Erectile Function (EF) domain scores categorized according to the classification proposed by Cappelleri *et al.* (1999).

Patients were eligible if they: (i) were aged ≥18; (ii) were able to provide a thorough medical and sexual history; and (iii) agreed to complete the psychometric instrument.

A total of 124 men were excluded because they lacked one or more of the entry criteria: a detailed medical history was not evaluable (n = 76; 8.6%) or IIEF compilation was incomplete or imprecise (n = 48; 5.4%). A final sample of 757 patients (85.9%) was included in the analyses.

Data collection was performed following the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to deliver their own anonymous information for future studies.

Main outcome measures

The primary end point was to assess whether sexual functioning, as objectively defined with the IIEF domain scores, is associated with health-significant comorbidities, as scored with the CCI, even irrespective of CV risk factors.

Statistical analyses

Data are presented as median [quartile] unless otherwise indicated. Descriptive statistics and one-way analysis of variance (ANOVA) with Tukey post hoc analysis for multiple comparisons assessed the association between IIEF domain scores and CCI or CCI-CV scores. Binomial logistic regression models tested the predictive ability of categorical variables. Two models were developed: in model 1, all IIEF domains score were considered separately; conversely, model 2 included the IIEF-total score. Statistical tests were performed using SPSS v.20 (IBM Corp., Armonk, NY, USA). All tests were two-sided, with a significance level set at 0.05.

RESULTS

Table 1 lists patient demographic characteristics and descriptive statistics. Mean age of the entire cohort was 47.8 years; overall, 164 (21.6%) patients had a CCI ≥ 1. After CCI rescoring, 138 (18.2%) patients had a CCI-CV ≥ 1. Moreover, 200 (26.4%) patients had hypertension. Comorbidities according to their diagnostic categories and the ICD-9-CM codes are available in Table S1. Likewise, Table S2 lists the drugs taken by every patient according to CCI score and segregated by family of drugs.

As a whole, ED was the most frequently reported sexual complaint, followed by PE, Peyronie's disease, and LSD/I (Table 2). Of all, 268 (35.4%) patients complained of multiple and concurrent sexual disorders (Table 2). When stratified for IIEF-EF

severity, 578 (76.3%) patients had ED, with as many as one out of three men with scores suggestive of severe ED (Table 2).

Table 3 depicts the findings of the ANOVA tests. IIEF-EF was significantly reduced as a function of incremental CCI scores (Table 3A). Likewise, IIEF-EF significantly decreased as a function of incremental CCI-CV scores (Table 3B). Similarly, both the IIEF-Intercourse satisfaction (IIEF-IS) domain and the IIEF-total score significantly decreased along with an increased number of comorbidities, both considering CCI and CCI-CV scores (Table 3A,B, respectively).

At UVA logistic regression analysis (Table 4A), age, BMI, hypertension, IIEF-EF, IIEF-IS, IIEF-orgasmic function (IIEF-OF), and IIEF-total score accounted for CCI ≥ 1 (all $p \leq 0.01$). Similarly, age, BMI, hypertension, IIEF-EF, IIEF-IS, IIEF-OF, and IIEF-total score also accounted for higher CCI-CV ≥ 1 (Table 4B; all $p \leq 0.01$). Table 4A,B also depict the findings of the MVA logistic regression analyses for both CCI and CCI-CV. In this context, IIEF-EF and IIEF-total scores achieved independent predictor status for both CCI and CCI-CV scores ≥1, even after adjusting for potential confounders (all $p \leq 0.04$; Table 4A,B, respectively).

DISCUSSION

We analyzed the relationship between ED and overall men's health, as objectively measured with a reliable and widely used index scoring a large number of comorbid conditions. Current novel findings showed that in a homogenous cohort of sexually active, Caucasian-European men with new-onset sexual dysfunction, the severity of ED, as interpreted with a validated psychometric instrument, was significantly correlated with the burden of comorbidities even irrespective of any type of CVD.

Erectile dysfunction is an established CV risk factor, with numerous piece of information demonstrating a significant correlation between ED and CVDs (Guo *et al.*, 2010; Dong *et al.*, 2011; Vlachopoulos *et al.*, 2013; Gandaglia *et al.*, 2014) even

Table 1 Patient characteristics and descriptive statistics ($n = 757$)

Age (years)	
Median	48
IQ range	37–59
BMI (kg/m^2)	
Median	25
IQ range	23.1–27.4
CCI score	
Median	0.0
Range	0–0
CCI [No. (%)]	
Score 0	593 (78.3)
Score 1	66 (8.7)
Score ≥2	98 (12.9)
CCI-CV [No. (%)]	
Score 0	619 (81.7)
Score 1	59 (7.8)
Score ≥2	79 (10.4)
Hypertension [No. (%)]	200 (26.4)
Smoker [No. (%)]	
Yes	279 (36.9)
No	478 (63.1)
Regular physical activity [No. (%)]	
Yes	403 (53.3)
No	354 (46.7)

BMI, body mass index; CCI, Charlson Comorbidity Index; CV, cardiovascular diseases; IQ range, interquartile range.

Table 2 Reported sexual dysfunctions and psychometric characteristics of the entire cohort

Sexual complaints [No. (%)][a]	
ED	540 (71.4)
PE (either LL or acquired)	157 (20.8)
LSD/I (either primary or acquired)	168 (22.2)
Peyronie's disease	137 (18.2)
Multiple concomitant sexual dysfunctions	268 (35.4)
ED + PE	90 (11.8)
ED + Peyronie's disease	69 (9.1)
ED + LSD/I	131 (17.3)
IIEF domains	
IIEF-EF score	
Median	17.0
IQ range	7–25
IIEF-IS score	
Median	8.0
IQ range	3–11
IIEF-OF score	
Median	9.0
IQ range	5–10
IIEF-SD score	
Median	7.0
IQ range	6–8
IIEF-OS score	
Median	5.0
IQ range	3–8
IIEF-total score	
Median	43.0
IQ range	25–58
ED severity [No. (%)]	
No ED	179 (23.7)
Mild	122 (16.1)
Mild-to-moderate	94 (12.4)
Moderate	105 (13.9)
Severe	257 (33.9)

ED, erectile dysfunction; PE, premature ejaculation; LSD/I, low sexual desire/interest; IIEF, International Index of Erectile Function; EF, Erectile Function domain; IS, intercourse satisfaction domain; OF, orgasmic function domain; SD, sexual desire domain; OS, overall satisfaction domain; IQ range, interquartile range.
[a]Patients with multiple sexual complaints were reported in more than one category.

Table 3 (A) One-way analysis of variance (ANOVA) with Tukey post hoc analysis of the IIEF domain scores [mean (SD)] according to CCI (categorized as 0 vs. 1 vs. ≥2). (B) One-way analysis of variance (ANOVA) of the IIEF domain scores [mean (SD)] according to CCI-CV (categorized as 0 vs. 1 vs. ≥2)

(A) IIEF domains	CCI = 0	CCI = 1	CCI ≥ 2	*F*	*p*-value
IIEF-EF	17.57 (9.2)*	14.15 (9.66)*	10.34 (8.15)*	28.5	<0.01
IIEF-IS	7.22 (4.58)*	6.71 (4.81)	5.84 (4.81)*	3.49	0.03
IIEF-OF	7.36 (3.28)*	6.56 (4.08)	5.58 (3.76)*	10.9	<0.01
IIEF-SD	6.99 (2.14)	6.68 (2.25)	6.78 (2.25)	0.79	0.45
IIEF-OS	5.49 (2.59)	5.31 (2.93)	4.98 (2.85)	1.49	0.22
IIEF-total	43.1 (18.7)	36.5 (21.4)	31.2 (18.9)	18.1	<0.01
(B) IIEF domains	CCI-CV = 0	CCI-CV = 1	CCI-CV ≥ 2	*F*	*p*-value
IIEF-EF	17.42 (9.24)*	13.19 (9.30)*	10.24 (8.36)*	25.28	<0.01
IIEF-IS	7.17 (4.58)*	6.43 (4.75)	6.04 (4.99)*	2.26	0.10
IIEF-OF	7.30 (3.33)*	6.82 (3.87)	5.37 (3.77)*	10.1	<0.01
IIEF-SD	6.99 (2.14)	6.67 (2.05)	6.68 (2.38)	1.06	0.62
IIEF-OS	5.46 (2.60)	5.27 (2.85)	5.07 (2.92)	0.78	0.45
IIEF-total	42.7 (18.8)	35.2 (20.9)	30.9 (19.4)	16.4	<0.01

IIEF, International Index of Erectile Function; EF, Erectile Function domain; IS, intercourse satisfaction domain; OF, orgasmic function domain; SD, sexual desire domain; OS, overall satisfaction domain; CCI, Charlson Comorbidity Index; CV, cardiovascular risk factors. *$p < 0.05$ at Tukey post hoc test between marked groups.

Table 4 Univariable and multivariable binomial logistic regression logistic regression analyses predicting CCI ≥ 1 (A) and CCI-CV ≥ 1 (B) and including as covariates: age, BMI, HPT, smoking, PA, IIEF domains, and total score

	(A)		
	UVA for CCI OR; *p*-value (95% CI)	MVA for CCI (model 1) OR; *p*-value (95% CI)	MVA for CCI (model 2) OR; *p*-value (95% CI)
Age	1.09; <0.01 (1.07, 1.11)	1.08; <0.01 (1.05, 1.10)	1.08; <0.01 (1.06, 1.10)
BMI	1.06; 0.01 (1.01, 1.11)	1.01; 0.60 (0.95, 1.08)	1.01; 0.85 (0.95, 1.06)
HPT	3.43; <0.01 (2.37; 4.95)	2.15; 0.002 (1.31, 3.53)	1.94; <0.01 (1.25, 3.02)
Smoking	0.78; 0.18 (0.54; 1.12)	1.06; 0.79 (0.66, 1.69)	0.97; 0.90 (0.63, 1.49)
PA	0.83; 0.30 (0.58; 1.17)	1.12; 0.60 (0.71, 1.77)	1.06; 0.60 (0.71, 1.59)
IIEF-EF	0.93; <0.01 (0.91, 0.95)	0.85; 0.04 (0.73, 0.99)	–
IIEF-IS	0.95; 0.01 (0.91, 0.99)	1.04; 0.63 (0.86, 1.27)	–
IIEF-OF	0.89; 0.01 (0.85, 0.94)	0.93; 0.37 (0.79, 1.09)	–
IIEF-SD	0.94; 0.21 (0.87, 1.03)	1.01; 0.93 (0.83, 1.22)	–
IIEF-OS	0.94; 0.11 (0.88; 1.01)	1.05; 0.46 (0.74; 1.20)	–
IIEF-total	0.97; <0.01 (0.96, 0.98)	–	0.97; <0.01 (0.96, 0.98)
	(B)		
	UVA for CCI-CV OR; *p*-value (95% CI)	MVA for CCI-CV (model 1) OR; *p*-value (95% CI)	MVA for CCI-CV (model 2) OR; *p*-value (95% CI)
Age	1.08; <0.01 (1.06, 1.10)	1.07; <0.01 (1.04, 1.09)	1.07; <0.01 (1.04, 1.09)
BMI	1.05; 0.02 (1.01, 1.10)	1.02; 0.47 (0.95, 1.06)	1.01; 0.95 (0.95, 1.07)
HPT	2.55; <0.01 (1.73, 3.77)	1.02; 0.08 (0.93, 2.61)	1.46; 0.10 (0.92, 2.31)
Smoking	0.73; 0.12 (0.49, 1.08)	0.90, 0.68 (0.55, 1.47)	0.87, 0.54 (0.55, 1.36)
PA	0.89; 0.57 (0.62, 1.30)	1.21; 0.40 (0.76, 1.94)	1.15; 0.50 (0.75, 1.76)
IIEF-EF	0.93; <0.01 (0.91, 0.95)	0.89; <0.01 (0.85, 0.93)	–
IIEF-IS	0.95; 0.03 (0.91, 0.99)	1.10; 0.04 (1.01, 1.22)	–
IIEF-OF	0.90; <0.01 (0.85, 0.95)	0.99; 0.86 (0.91, 1.08)	–
IIEF-SD	0.93; 0.14 (0.85, 1.02)	1.01; 0.76 (0.90, 1.14)	–
IIEF-OS	0.95; 0.23 (0.88, 1.03)	1.10; 0.17 (0.95, 1.26)	–
IIEF-total	0.97; <0.01 (0.96, 0.98)	–	0.97; <0.01 (0.96, 0.98)

CCI, Charlson Comorbidity Index; CV, cardiovascular risk factors; BMI, body mass index; HPT, hypertension; PA, physical activity; IIEF, International Index of Erectile Function; EF, Erectile Function domain; IS, intercourse satisfaction domain; OF, orgasmic function domain; SD, sexual desire domain; OS, overall satisfaction domain; OR, odds ratio.

irrespective of age, as it was demonstrated by data showing a higher risk for subsequent CV events in younger as compared with older men (Vlachopoulos *et al.*, 2013; Rastrelli *et al.*, 2014). Therefore, the most updated current international recommendations clearly stress the clinical importance of a CVD screening in every patient presenting with ED; this could consider the Framingham Risk Score (FRS) calculation for an initial CV risk stratification (Nehra *et al.*, 2012) or the coronary artery calcium test which shows how to better stratify ED patients according to their personal CV risk profile, as more recently suggested (Shah *et al.*, 2016). In this context, in a population of 965 men free of CVDs, Fang *et al.* (2015) showed that patients with a history of transient or persistent ED had a greater increase of the FRS over time, even regardless of common CV risk factors. In terms of pathophysiology, the occurrence of endothelial dysfunction at the level of penile vasculature has been suggested as one of the major links between ED and CVDs (Gandaglia *et al.*, 2014). Among others, the 'artery-size' hypothesis, which configures ED as an early manifestation of a generalized vascular endothelial disease, was the first to outline the impairment of erectile function as a possible real-life sentinel marker of co-existing and undetected CVDs (Montorsi *et al.*, 2003; Yao *et al.*, 2012). Thereafter, a number of studies supported the clinical concept behind that first theory, highlighting the importance of addressing the onset of ED several months well before a potential subsequent CV event of significant clinical relevance (Thompson *et al.*, 2005; Chew *et al.*, 2010; Vlachopoulos *et al.*, 2013). Given the extraordinary importance in the everyday clinical setting of these well-established data, the role of ED as a sentinel marker of risky disease has been further strengthened by the evidence of a correlation between ED and other comorbid conditions, with an impressive direct effect on men's overall health (Chung *et al.*, 2011; Salonia *et al.*, 2012; Banks *et al.*, 2013). To this regard, in a survey conducted on a cohort of 2213 men with ED as compared with 11,065 matching controls without the disorder, Chung *et al.* (2011) analyzed the prevalence and risk of 36 different comorbidities, showing an increased risk of metabolic disorders, gastrointestinal diseases, and chronic pulmonary diseases for men with ED. Likewise, ED was found to be the presenting symptom of diabetes mellitus (DM) for some men (Sairam *et al.*, 2001; Skeldon *et al.*, 2015); for instance, in a cohort of 1417 men, Skeldon *et al.* (2015) observed an overall prevalence of 11.5% of undiagnosed DM in men with ED which was significantly greater than the 2.8% prevalence observed in men without ED. These findings were further supported by the evidence that men younger than 40 years with ED showed higher levels of the insulin resistance-index, which has been previously associated with endothelial dysfunction; once more, this finding suggests that an early glycometabolic disorder may be the common ground fostering both ED and a particular subset of associated pathological conditions, thus including a subsequent DM (Skeldon *et al.*, 2015), this being correlation of even greater importance at younger ages. Moreover, in a population-based cohort from the Massachusetts Male Aging Study that has been observed over almost 15 years, ED was found to be a significant predictor of metabolic syndrome (MetS), with an unadjusted relative risk of 1.35 even in men with normal weight at baseline (Feldman *et al.*, 1994). A sustained systemic inflammation state, as an underlying potential reason for endothelial dysfunction, is considered the common pathological substrate between ED, MetS, and other

major comorbidities (Vlachopoulos *et al.*, 2006, 2007). To this regard, Vlachopoulos *et al.* (2006) showed that the IIEF-5 item score was inversely correlated with the serum levels of a number of endothelial prothrombotic and inflammatory factors, thus including the von Willebrand factor, fibrinogen, interleukin-1β, and interleukin-6. Similarly, a chronic higher level of circulating inflammatory mediators has been considered responsible for the correlation between ED and respiratory diseases, thus including chronic obstructive pulmonary syndrome and asthma (Vlachopoulos *et al.*, 2007; Carneiro *et al.*, 2010). In this context, Salonia *et al.* (2012) studied the correlation between ED severity and the general male health status in a cohort of 140 patients with new-onset ED in the real-life setting. Their findings showed a significant correlation between IIEF-EF scores and the burden of comorbid conditions as objectively interpreted with the CCI, thus providing novel evidence that ED severity may be linked with the overall sum of comorbidities. Current results confirm those latter previous findings, pointing out that both IIEF-EF and IIEF-total score achieved independent predictor status for higher CCI scores, even after adjusting the analyses for patient's age, BMI, cigarette smoking, and physical activity. We chose to use the CCI because this index was designed as a valid and applicable method of estimating risk of death from comorbid diseases, by applying different weighted scores to each comorbidity according to its prognostic impact. Moreover, it includes several CVDs which may eventually contribute to the final total score (Charlson *et al.*, 1987). In this context, the significant association between CVDs and ED could actually represent the main reason for ED severity and its eventual correlation with higher CCI scores. In order to better investigating the clinical importance of EF impairment over the whole health status of a man presenting for ED in the real-life scenario, we further considered the burden of his overall medical history regardless of CVDs, thus obtaining the CCI-CV. Of clinical importance, our findings provide novel evidence that both the IIEF-EF and the IIEF-total scores were independently and inversely correlated with higher CCI-CV scores, thus supporting the hypothesis that ED severity is significantly associated with comorbid conditions other than CVDs. Among them, ED emerged as an independent clinical marker of a number of respiratory disorders, connective tissue disorders, kidney and liver impairment, neurological diseases, and cancers. As a second major clinical finding, the correlation between the IIEF score and the burden of comorbidities was independent of age, thus confirming previous data showing a significant association in young individuals between severe ED and a higher risk of death from all causes, regardless of a history of CVDs (Banks *et al.*, 2013). Therefore, we believe that these findings should have a direct impact on the everyday clinical practice, prompting physicians to carefully screen for potential risky comorbid conditions in men complaining of severe ED even, and above all, regardless of the age of the individual.

Our study is not devoid of limitations. First, while these results could be representative of this relatively large homogenous cohort of sexually active, same-race men, it would deserve external validation with a larger independent sample. As noted in the Methods section, roughly 5% of the patients were excluded from the analysis because they produced incomplete IIEF questionnaires. It has been demonstrated that questionnaire-based analyses generally have a lower response rate than other types of investigations because men tend to be more reluctant to reveal ED and other impairments of intimate body functions when responding to questionnaires than when speaking directly to their physicians. However, questionnaire-based analyses allow for more critical and thus more valid and reliable results (Nicolosi *et al.*, 2006). Second, we have provided a detailed list of patient's medications which either could or not have an impact on erectile functioning, but arbitrarily they had been not included in the final analyses. Third, the study did not provide data related to the assessment of psychological distress and depression. To this regard, a number of studies have indicated that depression represents a possible risk and/or maintenance factor for male sexual disorders (Waldinger, 2015); moreover, mental health per se does represent a relevant part of overall men's health status and this might further limit the completeness of these findings. Similarly, the lack of the role of the hormonal milieu could have partially undervalued the validity of these results, given their potential role in the etiology and pathophysiology of both ED and other comorbid conditions. Fourth, for a more complete picture of factors related to overall health status, the current analysis also could have included patients' monthly income, socio-economic well-being, other non-included recreational habits (e.g. drugs abuse), and standard of living. Indeed, although only a few population-based ED studies have included income in their analyses, most found significant associations between income-derived standard of living and men's sexual health (Cheng *et al.*, 2007). However, we decided not to include this variable because of the low response rate we usually obtain on income questions in real-life clinical practice during standard office visits.

Finally, we recognize that the major methodological flaw comes from the cross-sectional design of the study itself, along with the lack of an adequate patient follow-up. In this context, although we cannot rely on ED as a perfect indicator of the subsequent development of major comorbidities, we may trust that ED is a sentinel marker for undetected risky diseases other than CVDs.

The role of ED as a sentinel marker of co-existing and undetected diseases has been historically investigated mainly in the field of CVDs. However, a significant correlation between ED and several major comorbidities outside the CV field has been widely reported, leading to the concept of ED as a proxy of general health. We have presented novel findings of a significant linear correlation between ED severity and the burden of comorbid conditions as scored with a reliable index of health-significant comorbidities such as the CCI score, even irrespective of CVDs. Of major clinical relevance, this correlation emerged to be independent of age, thus suggesting the need for a comprehensive assessment of every patient seeking medical help for ED in the real-life everyday clinical practice, because ED severity per se might indicate the presence of major unacknowledged risky diseases.

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All the authors declare that they have no potential conflicts of interest.

AUTHORS' CONTRIBUTIONS

Substantial contributions to research design: Andrea Salonia, Paolo Capogrosso, Francesco Montorsi; Substantial contributions to the acquisition of data: Roberta Scano, Eugenio Ventimiglia, Luca Boeri, Filippo Pederzoli, Walter Cazzaniga, Giorgio Gandaglia, Federico Dehò, Andrea Salonia; Substantial contributions to the analysis or interpretation of data: Paolo Capogrosso, Eugenio Ventimiglia, Umberto Capitanio, Andrea Salonia; Drafting the paper or revising it critically: Paolo Capogrosso, Francesco Montorsi, Andrea Salonia; Approval of the submitted and final versions: Paolo Capogrosso, Eugenio Ventimiglia, Luca Boeri, Umberto Capitanio, Giorgio Gandaglia, Federico Dehò, Filippo Pederzoli, Roberta Scano, Francesco Montorsi, Andrea Salonia.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Diagnostic categories, ICD-9-CM codes, and CCI weights within the whole cohort [No. (%)].

Table S2. Therapeutic drugs in patients with CCI = 0 and CCI ≥ 1.